CG ONCOLOGY

CRETO-EAP
EXPANDED ACCESS PROGRAM

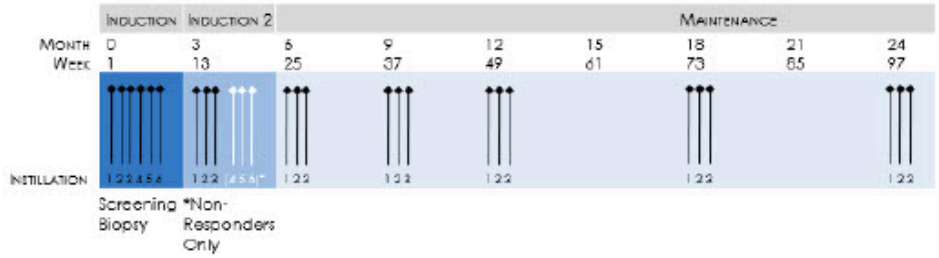
Cretostimogene Expanded Access Protocol (CRETO-EAP)

An Expanded Access Program of Cretostimogene Grenadenorepvec in Patients with Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG)

PROTOCOL NUMBER:	CRETO-EAP
INVESTIGATIONAL PRODUCT:	Cretostimogene Grenadenorepvec, DDM
INN NAME	Cretostimogene Grenadenorepvec
IND NUMBER:	12154
SPONSOR:	CG Oncology, Inc
SPONSOR CONTACT:	Andy Darilek, MD Andy.Darilek@CGOncology.com
MEDICAL MONITOR:	Andy Darilek, MD
PROTOCOL DATE:	18 April 2024
Amendment 1:	11 December 2024
Amendment 2	18 April 2025

PROTOCOL SYNOPSIS

Title:	An Expanded Access Program of Cretostimogene Grenadenorepvec in Participants with High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG)
Sponsor:	CG Oncology, Inc
Investigational Products:	Cretostimogene Grenadenorepvec: Engineered human adenovirus type 5 with an E2 transcription factor (E2F) promoter and human granulocyte-macrophage colony-stimulating factor (GM-CSF) DDM: n-dodecyl-β-D-maltoside
INN Name	Cretostimogene Grenadenorepvec
Phase:	Expanded Access
Objectives:	**Primary Objective:** • To determine the safety of cretostimogene in participants with Bacillus Calmette-Guerin (BCG)-unresponsive high-risk NMIBC, under an Expanded Access Program • To determine the Complete Response (CR) rate at any time of cretostimogene in participants with BCG-unresponsive CIS with or without high-grade (HG) Ta/T1 papillary NMIBC **Secondary Objectives:** • Assess duration of response (DoR) • Assess progression-free survival (PFS) • Determine cystectomy-free survival • Assess participant reported outcomes and health-related quality of life measures, via the European Organization for Research and Treatment of Cancer (EORTC) QLQ-NMIBC24, EuroQol EQ-5D-5L, Patient Global Impression of Change (PGI-C) and Patient Global Impression of Severity (PGI-S), Was It Worth It (WIWI), and Clinical Global Impression of Change (CGI-C)
Study Design Overview:	This is an open-label, expanded access trial designed to provide access to cretostimogene in participants with high-risk, non-muscle invasive bladder cancer (NMIBC) unresponsive to BCG. This protocol is designed to enroll up to 100 participants with CIS with or without concomitant HG Ta/ T1 papillary NMIBC.
Study Design:	Cretostimogene will be administered at a dose of 1×10^{12} viral particles (vp) intravesically (IVE) following instillation of 0.1% DDM. Cretostimogene will be administered every week for 6 treatments on Weeks 1, 2, 3, 4, 5, and 6. If the participant has persistent HG Ta and/or CIS at Week 13, the participant may receive another cycle of 6 weekly treatments on Weeks 13, 14, 15, 16, 17, and 18. If the participant has a complete response (CR) at Week 13, the participant will receive a cycle of 3 weekly treatments on Weeks 13, 14, and 15 (See Section 4.2, Response Definition). If the participant has persistent but improved HG Ta and/or CIS at Week 25 or a later timepoint, the participant may receive a repeat induction cycle of 3 weekly treatments of cretostimogene at the discretion of the Investigator (See Section 4.2, Response Definition) provided that T1 or higher stage of urothelial carcinoma is not present. If CR continues, participants will receive 3 weekly treatment cycles every 12 weeks through Week 51. After Week 51, participants will receive 3 weekly treatment cycles every 6 months through the last treatment cycle at Month 24 (Weeks 97, 98, and 99) or until the participant discontinues from the study treatment.

	 ***NOTE***: Cretostimogene treatment should begin at least 14 days after the most recent transurethral resection (TUR) or biopsy ***NOTE***: A minimum of 4 weeks is recommended between the last dose of a previous treatment cycle and the first dose of the next treatment cycle
Study Population:	**Inclusion Criteria:** To be eligible for participation in this expanded access trial, participants must meet all of the following entry criteria: 1. Be ≥18 years of age (or legal age of majority in the jurisdiction) on day of signing informed consent 2. Have Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 3. 3. Have pathologically confirmed (World Health Organization [WHO] grading system employed for tumor grading) (*Humphrey, 2016*) BCG-unresponsive CIS with or without HG Ta or HG T1 NMIBC. Participants with BCG-unresponsive CIS and concomitant low-grade (LG) Ta/T1 NMIBC are also eligible. 4. Have all Ta and/or T1 disease resected and all CIS resected or fulgurated, as feasible, prior to study treatment. 5. Received prior adequate BCG therapy defined as at least one of the following ("5+2" minimum exposure; all 7 qualifying doses should be greater than or equal to one third [1/3] of full dose BCG): a. At least 5 of 6 doses of an initial induction course (adequate induction) plus at least 2 of 3 doses of maintenance therapy, OR b. At least 5 of 6 doses of an initial induction course (adequate induction) plus at least 2 of 6 doses of a second induction course The "5+2" minimum BCG treatment should be completed within 15 months of the initial qualifying BCG induction dose, if feasible. 6. Ineligible to receive radical cystectomy (medically unfit) or refusal of radical cystectomy based on Investigator assessment. 7. Demonstrate adequate organ function, as evaluated by the Investigator in relevant laboratory parameters. CG Oncology reserves the right to review local laboratory results completed per standard of care. 8. Willing to use barrier contraception, as outlined in Section 9.2, during sexual activity, during the treatment period starting at least 7 days prior to Day 1 for women, and starting at Day 1 for men, through 1 week after the last dose of cretostimogene. **Exclusion Criteria:** The participant must be excluded from participating in the trial if the participant:

	1. Has current or past history of muscle invasive (T2 or higher stage) or locally advanced (T3/T4, any N) or metastatic bladder cancer. 2. Has received systemic anticancer therapy, including investigational agents, within 4 weeks of Day 1. ***NOTE:*** Participants who have entered the follow-up phase of an investigational study may participate if it has been at least 4 weeks after the last dose of the previous investigational agent. 3. Has had prior systemic treatment (excluding checkpoint inhibitor therapy), radiation therapy, or surgery for bladder cancer other than TURBT or bladder biopsies. 4. Has used excluded anti-viral medication (eg, interferon/peg-interferon, ribavirin, etc.) within 14 days of Day 1 and that cannot be suspended throughout for at least 14 days prior to and after each treatment with cretostimogene. 5. Requires use of anti-platelet or anti-coagulant therapy that cannot be safely suspended for standard of care procedures. 6. Has significant immunodeficiency due to underlying illness. Participants with human immunodeficiency virus (HIV), rheumatoid arthritis, and other autoimmune disorders may be considered on a case-by-case basis. 7. Has received systemic immunosuppressive medication including high-dose corticosteroids (eg, systemic corticosteroids >10 mg prednisone or equivalent), within 4 weeks prior to Day 1. ***NOTE:*** Participants must not be receiving doses of >10 mg/day of prednisone or equivalent at the time of study entry or during the study and corticosteroids may not be used for premedication ***NOTE***: Participants with contrast dye allergies may be given 1–3 dose(s) of a systemic steroid in order to complete a contrast-enhanced computerized tomography (CT) urogram for trial purposes. A 14-day minimum separation of the steroid dose and cretostimogene dose must occur. ***NOTE***: Participants may receive short courses (5-10 days) of steroids in doses greater than 10 mg/day or prednisone or equivalent to treat medical conditions, if indicated. Efforts should be made to separate high-dose steroids from cretostimogene dosing by as many days as possible. 8. Has had a prior organ transplant at any time or allogenic stem cell transplant within 3 years of study entry. 9. Has known active acute Hepatitis B (defined as HBsAg reactive) or Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection, or active chronic infection that requires anti-viral medications. 10. Participants with active acute or active chronic Hepatitis B or C, who take medications with anti-Hepatitis B or C activity are ineligible. Participants who have evidence of hepatic decompensation or decompensated cirrhosis on physical exam, laboratory, pathologic, or radiographic testing also are ineligible. Participants with inactive chronic Hepatitis B or C infection (asymptomatic healthy carriers) who have stable hepatic function are eligible for trial entry. Local labs may be requested for review (eg, AST, ALT, bilirubin, coagulation studies, CBC). ***NOTE:*** No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority. 11. Has current or prior pelvic (including the bladder) external beam radiotherapy within 2 weeks of entry.

	12. Has an active infection requiring systemic therapy that might interfere with the intravesical administration of cretostimogene (eg, urinary tract infection or other active infection). 13. Has had active autoimmune or inflammatory disease requiring systemic treatment within 4 weeks of Day 1 (ie, with use of disease modifying agents, prolonged high-dose corticosteroids, or immune-modulating drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered an excluded form of systemic treatment and is allowed. 14. Is pregnant, currently breastfeeding, or intending to breastfeed within the projected duration of the trial beginning at Screening through 6 weeks after the last study treatment 15. Has received a live vaccine within 30 days prior to the first dose of study drug.
Study Plan	**Screening:** Prior to the first day of cretostimogene treatment, the following standard of care procedures should be completed: • Urine cytology • Cystoscopy with directed biopsy of suspected areas of malignancy • Complete resection of all visible papillary (Ta or T1) tumor and fulguration and/or resection of detectable CIS, as feasible. • CT urogram or magnetic resonance urography (MRU) to assess for locally advanced or metastatic NMIBC, if required by local standard of care. **NMIBC Surveillance:** Every ***12-Week NMIBC Surveillance*** While on study treatment, participants will undergo routine NMIBC surveillance, including urine cytology and, as applicable, cystoscopy with directed biopsy of suspicious lesions. Additional evaluation may be performed at the discretion of the Investigator per local standard of care. **Low-Grade NMIBC at Any Timepoint (Complete Response):** If participants develop low-grade (LG) NMIBC at any time on study treatment, the LG lesion can be resected and the participant can continue study treatment. **Persistent NMIBC at the Week 13 Timepoint (Non-Response with Repeat Induction):** Participants with persistent CIS, HG Ta or CIS + HG Ta without T1 or higher stage urothelial carcinoma at Week 13 may continue study treatment (repeat induction) until the Week 25 evaluation timepoint at the discretion of the Investigator. **Persistent but Improved NMIBC at the Week 25 Timepoint (Partial Response):** Participants with persistent but improved CIS, HG Ta or CIS + HG Ta without T1 or higher stage urothelial carcinoma at Week 25 or subsequent timepoints who may, in the opinion of the Investigator, derive additional clinical benefit from continued cretostimogene administration are eligible to receive 3 additional doses of cretostimogene. **Cretostimogene and DDM Administration:** Participants can remain on study treatment for approximately 2 years in the absence of high-grade NMIBC recurrence without clinical benefit, progression of disease, unacceptable toxicity, or until Food and Drug Administration (FDA) approval of cretostimogene requires termination of the Expanded Access Program.

	The cretostimogene and DDM administration procedure is as follows: • Instillation of 100 mL 0.1% DDM for 15 minutes (±5 minutes) • Instillation of cretostimogene in up to 100 mL normal saline with 1 hour dwell time (±5 minutes) from time of complete instillation Details on dose preparation, storage conditions, and/or administration can be found in the *Cretostimogene Pharmacy Manual*, *Cretostimogene Instillation Manual*, and *Cretostimogene Intravesical Injection Preparation Worksheet*. **Pre-Treatment Considerations:** To ensure an adequate dwell time for cretostimogene and DDM, participants can be reminded to avoid caffeinated beverages and to minimize fluid intake for at least 4 hours prior to the start of the treatment. The bladder should be emptied of urine via catheter insertion prior to treatment, if feasible. Supportive care (eg, anticholinergic medications for bladder spasms) may be administered at the Investigator's discretion before or after treatment. **Post-Treatment Observation:** Participants should be monitored for at least 30 minutes following the first IVE treatment. Participant observation after subsequent treatments will be at the discretion of the Investigator. **Survival Follow-Up:** Participants who discontinue cretostimogene treatment for any reason will be contacted for survival (eg, telephone, email, in-person clinic visit) every 6 months for up to 2 years. If applicable, date and disease stage at the time of radical cystectomy or initiation of subsequent anticancer treatment will also be collected.
Procedures:	**Safety:** Safety data will be collected from Screening until 30 days after the last treatment with cretostimogene. Only serious adverse events (SAEs), Adverse Event of Clinical Interest (AECI) and Grade 3 or higher adverse events (AEs)or any stage event that leads to treatment or study discontinuation will be collected in the electronic case report form (\n 5.0).
Statistical Rationale and Analysis:	**Sample Size:** This expanded access trial will enroll up to 100 participants with BCG-unresponsive CIS with or without concomitant HG Ta/T1 papillary NMIBC. Enrollment may be increased if demand for expanded access is greater than the number of participants planned to be enrolled. Descriptive statistics (such as mean, median, standard deviation, and ranges for continuous data, and percentages for categorial data) will be used to summarize participant characteristics, treatment administration, efficacy, safety, and exploratory parameters. Data will also be displayed graphically, where appropriate.
Study Duration	**Estimated study accrual** (first participant in through last participant in): 18 months **Maximum study duration** per participant: 24 months ***NOTE***: Study accrual period and overall study duration may be reduced if FDA approval of a cretostimogene marketing application occurs. In the case of study termination due to regulatory marketing approval, active Expanded Access Program participants will be transitioned to commercially available cretostimogene therapy and offered enrollment in a registry program.